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(54) Title: PAROXETINE COMPOSITIONS AND PROCESSES FOR MAKING THE SAME

(57) Abstract: Paroxetine salt compositions having improved stability are formed by controlling the pH to 6.5 or less. The composi-  
tions can be made with the aid of water without significant coloration problems. The paroxetine salt include paroxetine hydrochloride  
salts but preferably use paroxetine sulfonate salts such as paroxetine methane sulfonate.

## PAROXETINE COMPOSITIONS AND PROCESSES FOR MAKING THE SAME

5

### CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority under 35 U.S.C. § 119(e) from prior U.S. provisional application serial no. 60/228,110 filed August 28, 2000 and from prior U.S. provisional application serial no. 60/234,936 filed September 26, 10 2000: the entire contents of each of the aforementioned provisional applications being incorporated herein by reference.

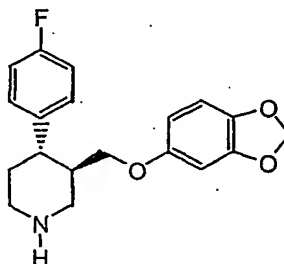
### BACKGROUND OF THE INVENTION

#### 15 1. Field of the Invention

The present invention relates to a paroxetine compositions, especially pharmaceutical formulations and dosage forms, and to processes of manufacturing the same.

#### 20 2. Description of the Related Arts

US Patent 4,007,196 describes certain compounds that possess anti-depressant activity. One specific compound mentioned in this patent is known as paroxetine and is represented by the following formula:

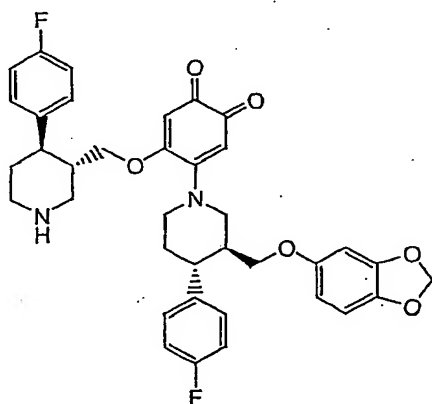


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Paroxetine has been approved for treating, *inter alia*, depression in humans and is being marketed around the world under such brand names as Paxil® (SmithKline Beecham) and Seroxat. Dosage forms thus far include immediate release

tablets, extended release tablets, capsules and suspensions. The active substance in all commercial forms thus far has been paroxetine hydrochloride and specifically with regard to tablets and other solid forms the active has been paroxetine hydrochloride hemihydrate as disclosed in US Patent 4,721,723 and EP 223403.

5 WO 95/16448 reports that all commercial paroxetine hydrochloride hemihydrate tablets were, at least up until that time, made using a wet granulation process. Further, the commercial tablets exhibited a color change; i.e., these tablets often developed a pink hue that is highly undesirable. This was apparently masked in the commercial product by a colored outer coat layer. The point of the PCT  
10 publication is that the pink hue formation can be avoided by carrying out tableting in the absence of water, i.e. by conventional dry granulation and direct compression. The PCT publication does not mention what the coloring compound(s) are or their route of formation. But, subsequent documents reveal that the coloration problem involves the formation of a coloring impurity identified below as the compound of  
15 formula A.



A

Since the publication of WO95/16448, it appears that the brand name  
20 paroxetine hydrochloride hemihydrate product in Europe, at least, was changed to a dosage form made by a dry granulation technique in accordance with the teachings in the PCT publication.

It would be advantageous to find a paroxetine composition that does not suffer from coloration or that is less prone to coloration regardless of how the composition is made. Further, it would be desirable to make a paroxetine composition with the aid of water, such as by wet granulation, that nonetheless was not prone to the above-mentioned coloration problems.

In particular, the application of an aqueous granulation process for industrial scale production is desirable in that such a process provides uniform distribution of the active substance within the bulk granulate composition so that the dose uniformity of tablets or capsules is more easily assured. This is especially true in the case of unit dosage forms containing a low dose of a potent active agent. Here, paroxetine is normally used in 20 to 40 mg per tablet and thus its uniformity in large scale production could be of concern. Water is a very suitable solvent for the granulation process because it is non-toxic and non-flammable. Thus, it would be desirable to find a way to use an aqueous granulation process for the industrial scale production of paroxetine final forms that would also avoid or limit the occurrence of the color forming impurities.

US Patent 5,874,447 describes paroxetine sulfonate salts, including paroxetine methane sulfonate also known as paroxetine mesylate. These sulfonate salts have advantageous properties in comparison to the known salts, including the hydrochloride salts. For example, the sulfonate salts have high water solubility and good thermal stability, making them useful in forming a commercial paroxetine dosage form. The 5,874,447 patent discloses that tablets can be made by any known method including a dry technique (direct compression, dry granulation) or a wet technique (wet granulation). However, no discussion appears in the 5,874,447 patent regarding the paroxetine hydrochloride coloring problem.

#### SUMMARY OF THE INVENTION

Now, it has surprisingly been discovered that solid paroxetine compositions including granulates and dosage forms made therefrom, can be made more stable against coloration, even if made with the aid of water such as by an aqueous granulation process, by controlling the pH of the composition to 6.5 or less.

Further, it appears that paroxetine sulfonate salts are less prone to coloration problems than paroxetine hydrochloride salts, even if made with the assistance of water. Studies by the present inventors reveal that the impurity A is a dimer formed from the paroxetine free base in an aqueous alkaline environment. Oxygen is also apparently  
5. needed to allow the dimer reaction to proceed. Given the discovery that coloring impurity A is formed in the presence of water, it is understandable in hindsight how carrying out a dry process as suggested in WO95/16448 would help to minimize and/or avoid coloration; i.e. the required aqueous medium for forming the dimeric impurity is missing thereby inhibiting its formation. Having elucidated the source of  
10 the coloring problem, the present invention provides a novel solution thereto by keeping the pH of the composition to 6.5 or less. Alternatively, the present invention unexpectedly solves the coloring problem by switching the paroxetine salt from hydrochloride to sulfonate and thereby allowing the use of water in the preparation of paroxetine granules without incurring any substantial coloration.

15 Thus, in a first aspect of the invention, there is provided a solid paroxetine composition comprising a paroxetine salt and an excipient wherein said composition has a pH of 6.5 or less, as is hereinafter defined. The paroxetine salt is preferably a paroxetine sulfonate salt such as paroxetine methane sulfonate or a paroxetine hydrochloride salt. The excipients generally include a binder or diluent  
20 such as calcium phosphate or microcrystalline cellulose as well as a disintegrant and lubricant. The composition can be an intermediate form or a final dosage form such as a tablet or capsule. In one embodiment, a tablet is made that does not need a taste masking coating to avoid the usual bitter taste associated with paroxetine compositions.

25 A second aspect of the present invention relates to paroxetine solid dosage forms comprising a paroxetine sulfonate salt as a pharmaceutically active agent and having been made with the aid of water. The solid dosage form can be a tablet, pellet or capsule form, etc., and contains a pharmaceutically effective amount of paroxetine sulfonate, e.g. for treating depression, obsessive-compulsive disorder, or  
30 panic attack, etc. Preferably the excipients are selected so that the composition has a pH of 6.5 or less. Further, the composition is normally dried to a sufficient extent that the total content of added water remaining is 2.0 wt% or less, preferably 1.3 wt% or less, and more preferably 1.0 wt% or less. Generally, the composition does not

contain any decolorization agent as an excipient. Even though an aqueous process is used, the dosage form of the present invention exhibits no, or substantially no, formation of a pink or other colored hue.

A third aspect of the invention provides for a granulate formed by

5 mixing water, paroxetine sulfonate salt, and at least one excipient and drying the resulting mixture. Typically the water and paroxetine sulfonate salt are provided together as an aqueous solution and added to the powdered or dry excipient(s), although this is not required. In some embodiments, the excipient(s) may be pre-

10 blended and granulated such as by a dry granulation technique before being contacted with a concentrated aqueous paroxetine sulfonate salt solution. The mixture is dried to form a granulate to which additional excipients may be added, if desired. The granulate can be formed into other conventional dosage forms such as tablets, capsules, sachets, pellets, etc. The composition is preferably selected as described above for the dosage forms, namely with a pH of 6.5 or less and with an added water

15 content of 2.0 wt% or less.

A fourth aspect of the invention provides a process for making

pharmaceutical compositions which comprises mixing paroxetine sulfonate and at least one excipient with the aid of water. In one convenient embodiment, an aqueous solution containing at least 10 wt % of a paroxetine sulfonate salt is added to at least

20 one solid excipient and dried to form a granulate. Preferably, the aqueous solution is a highly concentrated aqueous solution of paroxetine sulfonate salt having a concentration of not less than 30 wt%. This process can be used advantageously to form the granulates described above which can be subsequently processed into the above-described dosage forms. Alternatively, water can be added to a powder bed of

25 paroxetine sulfonate and one or more excipients and the mixture dried to form granules.

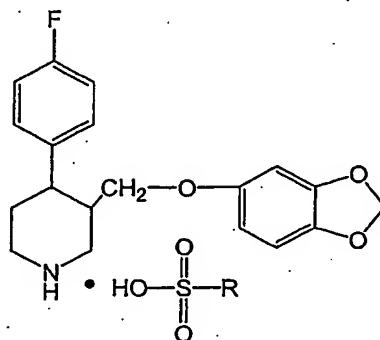
A preferred paroxetine sulfonate salt for use in all aspects of the present invention is paroxetine methanesulfonate, also called paroxetine mesylate. Paroxetine mesylate is compatible with many common pharmaceutical excipients useful in

30 aqueous granulation procedures, which makes the process reliable on an industrial scale.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to solid paroxetine compositions that resist the formation of a color hue and to processes for making the same with the aid of water. As used herein, the expression "made with the aid of water" means that water is added during some aspect of the formation process of the composition but is substantially or completely removed in the final composition. The water can be added to excipients, to the paroxetine salt especially paroxetine sulfonate salts, or to both. The solid compositions of the invention include solid dosage forms such as tablets, capsules, sachets, etc., and intermediate forms such as granules or pellets.

Paroxetine salts used in the present invention are pharmaceutically acceptable salts, i.e., acid addition salts. Preferred salts include paroxetine hydrochloride salts and paroxetine sulfonate salts. The paroxetine hydrochloride salt can be of any form including the paroxetine hydrochloride hemihydrate form and paroxetine hydrochloride anhydrate forms. The paroxetine sulfonate salts used in the present invention can be any salt of paroxetine where the anion contains a sulfonate group; i.e. the moiety  $-S(O_2)OH$ . Preferred sulfonate salts include those having the following structural formula:



wherein R represents a C<sub>1</sub> - C<sub>10</sub> substituted or unsubstituted alkyl group or a substituted or unsubstituted aromatic group wherein the substituents are selected from the group consisting of C<sub>1</sub> - C<sub>10</sub> alkyl, halogen, nitro, hydroxy, alkoxy, and combinations thereof. Preferred paroxetine sulfonate salts include those having a solubility in water of at least 100 mg/1 ml of water. Particularly preferred sulfonate salts include methanesulfonate, ethanesulfonate, benzenesulfonate and p-toluenesulfonate salt forms.

An "excipient" as used herein means any pharmaceutically acceptable inactive component of the composition. As is well known in the art, excipients include diluents, binders, lubricants, disintegrants, colorants, preservatives, pH-adjusters etc. The excipients are selected based on the desired physical aspects of the final form: e.g., obtaining a tablet with desired hardness and friability, being rapidly dispersible and easily swallowed, etc. The desired release rate of the active substance from the composition after its ingestion also plays a role in the choice of excipients.

Suitable excipients for use in this invention include:

- a diluent such as calcium hydrogen phosphate, lactose, mannitol etc.
- a binder such as microcrystalline cellulose or a modified cellulose, povidone etc.
- a disintegrant such as sodium starch glycollate, crosspovidone
- a lubricant such as magnesium stearate, sodium stearyl fumarate
- a colorant, taste masking agent etc..

It is particularly advantageous that the composition of the invention is not specifically required to use anhydrous excipients or hydrophobic excipients, although such excipients may be used. Similarly, the present invention does not have to strictly control the water content in the excipients prior to their use or incorporation. In a preferred embodiment, no decolorization agent is required to be present in the composition of the invention, although such may be present if desired. "Decolorization agent" as used herein means an agent which is being added to a composition with the aim to protect the active substance against reactions that form colored products, such as an antioxidant (e.g. ascorbic acid etc.), free radical scavenger (e.g. tocopherol etc.) etc.

It has now been discovered that the undesired impurity A is preferentially formed in an aqueous alkaline environment from the paroxetine free base. Accordingly, it can be advantageous to employ multiple strategies to reduce or prevent coloration. These strategies include limiting the amount of added water remaining in the composition, controlling the pH of the composition to be sufficiently acidic, limiting the presence of oxygen during formation and/or storage, and reducing



the level of paroxetine free base impurity in the active. Indeed, using one or more of these strategies can control the coloring problem encountered with other paroxetine salt forms including paroxetine hydrochloride salt forms, whether made from a dry or wet process. For example controlling the pH to 6.5 or less, controlling (reducing) the level of free base impurity, and/or quickly removing 98% or more of the water used in granulating should allow for the formation of a color stable paroxetine hydrochloride pharmaceutical composition. Additionally, for reasons that are not entirely clear, paroxetine sulfonate salts can provide superior color stability in comparison to paroxetine hydrochloride salts.

10           The compositions of the present invention, including granulates and final dosage forms, preferably have a pH of 6.5 or less, more preferably a pH of 6.0 or less, including about 5.5 or less. Typically, the pH of the dosage form or a granulate is within the range of 4.5 to 6.5, more typically from 5.0 to 6.0. The pH is determined by forming a slurry of the solid composition with water and measuring the pH of the slurry, as is understood by workers skilled in the art regarding the pH of a solid composition. The concentration of the composition in the slurry is 20 wt%. The pH is measured by any standard technique. The pH can be adjusted by the proper selection of excipients.

          In this respect, a proper grade of calcium phosphate (anhydrous or hydrated) having a pH around 5.5 is preferred to be used as a suitable filler. Commercially available/pharmaceutically acceptable calcium phosphates are generally alkaline; i.e. pH greater than 7 when measured as described above in a 20% slurry. For instance, DI-TAB, a commercially available dibasic calcium phosphate dihydrate, is reported as having a pH of about 7.4. Nonetheless some forms and grades of calcium phosphate are acidic or neutral pH. This lower pH can be due to the species of calcium phosphate as well as the treatment during processing of the material, such as in removing impurities/washing. For example, dibasic calcium phosphate anhydrate is generally considered to have a pH of about 7.3 whereas A-Tab<sup>TM</sup> (Rhodia), also a dibasic calcium phosphate anhydrate, has a pH of about 5.1.

25           Further examples of commercially available non-alkaline calcium phosphates include DiCAFOS P (Budenheim) having a pH of about 7 and Fujicalin SG (Fuji) having a pH from 6.1-7.2. By using a non-alkaline calcium phosphate as an excipient, a pharmaceutical composition meeting the desired pH can be attained. Alternatively, a

blend of calcium phosphates, even one using acidic and alkaline calcium phosphates, can be used to achieve the desired acidic pH of the composition. The pH can also be assisted by selection of any other excipients in the composition. For instance, another example of a useful acidic excipient is the disintegrant Explotab(TM) of Penwest, which is a cross-linked, low substituted sodium starch glycollate.

Especially advantageous compositions of the invention comprise paroxetine sulfonate salt in the absence of a hydrosoluble or hydrophilic diluent such as lactose or microcrystalline cellulose. Unlike the suggestions in CH 690 024, wherein such a hydrosoluble/hydrophilic diluent is taught for use with paroxetine mesylate, it has been discovered that surprisingly the use of only a calcium phosphate diluent, such as calcium hydrogen phosphate anhydrate, exhibits an additional advantageous feature for industrial application; namely that it efficiently masks or prevents the bitter taste of paroxetine. Thus, after the paroxetine salt, especially paroxetine mesylate, and diluent composition is mixed with a disintegrant and a lubricant and compressed into tablets, the tablets may be administered to a human patient without need of a taste-masking coating or a similar tool for taste masking. To the contrary, the presence of a hydrosoluble or hydrophilic diluent rather pronounces the bitter taste of paroxetine so that such tablet is unpleasant to be swallowed unless film-coated. Pharmaceutical compositions comprising paroxetine methane sulfonate and calcium hydrogen phosphate, optionally containing conventional lubricants and/or disintegrants, form a particular aspect of our invention. Of course, these particular compositions can be made by a dry process (dry mixing followed by direct compression) as well as by any of the wet processes known or described herein, and still provide the unexpected taste masking result.

In general, the compositions of the present invention preferably have a remaining added water content of 2.0 wt% or less, preferably 1.3 wt% or less, more preferably 1.2 wt% or less, still more preferably 1.0 wt% or less, and most preferably 0.8 wt% or less. The "remaining added water" content refers to the remaining water that was added in the aid of mixing and does not include water that was present in the excipients such as bound water in microcrystalline cellulose. If the composition was made by a dry process, then the remaining added water content is 0.0%. Generally, each formulation has a threshold amount of remaining added water content below which the dimeric impurity A is formed either very little or not at all. Above this

threshold amount, the impurity A is formed abundantly. The occurrence of the impurity is thus not usually a linear function of water content. By controlling the added water content in the final granulate, a color stable product can be attained, even if made by a conventional wet granulation process. The same is true for the final  
5 product solid dosage form.

Granules made according to the present invention can be used directly but usually are processed into any of a variety of dosage forms as mentioned above. Typically, the granules, optionally with additional excipients, are compressed into tablets. The paroxetine tablets may be coated by a suitable film-coating, e.g., similar  
10 to the coating used in the commercially available tablets of paroxetine hydrochloride hemihydrate. Suitable techniques of coating include aqueous coating, non-aqueous coating or a melt coating process. Coating mixtures are commercially available. Coating for extended or delayed release of the active substance is also applicable to the composition of our invention. Coating mixtures may contain suitable colorants.

15 The paroxetine-containing granulate may also be used for preparation of capsulized unit dosage forms. The dry granulate may be optionally screened and/or pelletized by methods known per se to obtain particulate material of uniform size and shape. The granules or pellets are then filed into suitable capsules made from e.g. gelatine, hydroxypropylmethyl cellulose or starch. Capsules having low moisture  
20 content are preferred. Coating of the produced granulate is normally not necessary.

Paroxetine-containing granulate may also be filled into sachets containing the required unit dose of paroxetine. Such sachets are administered by dispersing or dissolving the content thereof in a suitable liquid, e.g. in water, and drinking. The compositions may contain suitable taste-masking excipients, flavors or  
25 sweeteners.

Another suitable final form comprising granulates according to the present invention are effervescent tablets, granulates or powders. They are formed by mixing the granulate with a suitable effervescent system by methods known per se.

The compositions of the present invention can be made by any  
30 conventional process including dry process such as dry blending, dry granulation, and direct compression as well as by wet processes such as wet granulation. In some

embodiments, especially for paroxetine sulfonate salts, it is preferable to use water in the aide of mixing. For example, a granulate is formed by combining a paroxetine sulfonate salt and at least one excipient and mixing them in the presence of added water, followed by drying to remove substantially all of the added water. The  
5 resulting population of granules, or the "granulate," is dried to have a an average content of remaining "added water" of 2.0 wt% or less, preferably 1.3 wt % or less, more preferably 1.0 wt % or less and even 0.8 wt % or less, based on the total weight of the granulate.

Typically the water is added in one of two ways, although the invention  
10 is not limited thereto. In a first method, water is added to paroxetine sulfonate and an excipient. The amount of water added is normally between 5 and 25 wt %, more typically between 10 and 20 wt%, based on the total weight of the resulting wet mixture. More water can be added, i.e., 30 wt %, 40 wt% or even 50 wt%, but some difficulties may be encountered concerning possible modifications of the excipient  
15 (for instance microcrystalline cellulose may change crystal form) and additional energy will be needed to remove the higher amounts of added water. The paroxetine sulfonate salt and the excipient are normally in powder form and pre-mixed or blended to form a powder bed prior to the addition of water. Alternatively, the excipient can be in granulate form and admixed with the paroxetine sulfonate powder.  
20 The excipient is generally one or more diluents such as calcium phosphate, microcrystalline cellulose, or both.

The wet mixture is stirred, usually under vigorous conditions, to form a homogeneous mixture. The added water is removed from the wetted mixture normally as rapidly as possible. The added water can be removed by heating as well  
25 as by passing a nitrogen gas stream over (or through) the mixture, or a combination thereof. The use of a nitrogen gas stream is also advantageous in that the presence of oxygen is reduced or avoided. The drying of the added water can occur after, during or simultaneously with the mixing/stirring step. To reduce the chance of color formation, the average residence time of the added water in contact with the  
30 paroxetine sulfonate and excipient(s) during the mixing and drying steps is generally less than 3 hours, more typically less than 2 hours, more typically less than 1.5 hours, frequently less than or equal to 1 hour and is normally in the range of 30 to 90 minutes, more preferably 30 to 60 minutes, depending upon the apparatus volumes,

etc. Upon completion of the stirring and drying steps, a paroxetine sulfonate-containing granulate is obtained having a low added water content as described above.

For preparation of a final mixture for compressing into a tablet core (pre-compression mixture), the above paroxetine sulfonate-containing granulate is optionally mixed with additional diluent(s), a disintegrant and/or a lubricant such as magnesium stearate, in a suitable mixer, e.g. in a free-fall mixer. The pre-compression mixture is finally compressed into tablets by a suitable tableting press under ordinary conditions. The other excipients for mixing with the granulate should also be chosen, in terms of kind and grade, such that the final pre-compressing mixture exhibits a pH value of 6.5 or less as described above.

A second method for forming the granulate involves combining the added water with the paroxetine sulfonate to form an aqueous solution of paroxetine sulfonate. This aqueous solution is then added to at least one excipient. As in the first method, the excipient can be in powder or granulate form. The aqueous solution is generally a concentrated solution having at least 10 wt% paroxetine sulfonate, preferably at least 30 wt%, and more preferably at least 40 wt% paroxetine sulfonate. By using a concentrated solution, less water is needed, thereby saving energy in the drying step and allowing for faster drying times. These highly concentrated solutions are possible because of the advantageous water solubility of paroxetine sulfonate in comparison to other paroxetine salts such as paroxetine hydrochloride. The stirring and drying steps as well as the work up of the granulate into a pre-compression composition are carried out as described above.

A preferred formulation made by this process comprises adding the concentrated paroxetine sulfonate aqueous solution to either calcium hydrogen phosphate or microcrystalline cellulose followed by stirring and drying to form a paroxetine-containing granulate. To the formed granulate is then mixed the other one of the calcium hydrogen phosphate or microcrystalline cellulose which was not used to form the granulate along with sodium starch glycolate (a disintegrant) and magnesium stearate. The resulting mixed composition is ready for compression into tablets. An example of this composition contains 7.24 wt% paroxetine sulfonate (as the equivalent free base), 57.76 wt% of  $\text{CaHPO}_4$ , 30.0 wt% microcrystalline cellulose (Avicel PH 101), 4.0 wt % sodium starch glycolate, and 1 wt% magnesium stearate.

In the aqueous granulation procedure for preparation of tablets or capsules of paroxetine mesylate, microcrystalline cellulose and various forms and grades of calcium phosphate, typically calcium hydrogen phosphate, are the preferred solid diluents. However, the composition of this invention and the process for its preparation is not limited thereto. Alternate diluents include mono- and di saccharide  
5 sugars such as lactose, mannitol, lactitol, xylitol or combinations thereof.

Alternatively, a dry process can also be carried out wherein the paroxetine salt is dry blended with an excipient, typically a calcium phosphate or microcrystalline cellulose, or both and optionally with a disintegrant. After blending,  
10 the mixture is compressed into a tablet.

For both wet and dry processes, it is sometimes advantageous to provide multiple mixing steps to facilitate high quality, homogenous mixing. For example, a portion of the binder(s) and/or disintegrant(s) are mixed with the paroxetine salt, optionally with the aide of water as described above. To this mixture  
15 the remainder of the binder(s) and/or disintegrant(s) are mixed. To this resulting mixture the remaining excipients such as a lubricant(s) are mixed. Such partial mixing can use more steps or fewer steps and can split intermediate mixtures into portions to facilitate apparatus volumes. Additionally, excipients can be pre-treated by techniques known in the art as desired, including wet granulation and dry  
20 granulation treatments. The binders or fillers such as calcium phosphate anhydrate can be pretreated with water and dried (<0.5% water) before being combined with the paroxetine salt or solution.

The composition of the present invention can be used to treat or prevent the following disorders: depression, obsessive compulsive disorder, alcoholism, anxiety, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia,  
25 anorexia, social phobia, pre-menstrual syndrome, adolescent depression, trichotillomania, dysthymia, substance abuse etc. Most suitably, the composition of the invention is applied for treatment of depression, obsessive compulsive disorder and panic disorder.

The treatment or prevention of any one or more of the above disorders is performed by administering orally the composition comprising an effective and/or prophylactic amount of the paroxetine sulfonate to a patient in need thereof. The patient can be a mammal including a human, a dog, a horse, or a monkey.

- 5           The composition of this invention is advantageously presented as a unit dose composition, preferably in a form of a tablet or a capsule, comprising paroxetine sulfonate equivalent to from 1 to 200 mg of paroxetine free base, more usually from 5 to 100 mg, for example from 10 to 50 mg. Typical tablet doses are 10, 20, 30, and 40 mg. Such a composition is normally taken by a human patient from 1 to 6 times daily, 10 but more usually once or twice daily, with the total amount of paroxetine sulfonate administered being generally between 5 to 400 mg of paroxetine. A suitable daily dose is from 0.05 to 6 mg/kg, more preferably 0.14 to 0.86 mg/kg.

### Examples

15

#### Example 1

##### Granulate of Paroxetine mesylate for tablet production

1. Prepare a pre-blend of 3177.5 g of calcium hydrogen phosphate anhydrate (A-TAB pH 5.1) and 29.75 g of sodium starch glycolate by mixing for 5 minutes in a high-shear granulator.
2. Prepare a solution of 258.3 g of paroxetine mesylate in 350 ml of water.
3. Add the solution to the pre-blend granulate from the step 1 at ambient temperature.
4. Dry the wet granulate at 40 °C under diminished pressure and nitrogen flow to less than 1% water content.
- 25 5. Mix the resulted granulate with 29.75 g of sodium starch glycolate for 15 minutes in a free-fall mixer; add 70.0 g of magnesium stearate to the mixture and mix for 5 minutes.

30           Tablet cores containing 40 mg of paroxetine are prepared from the resulting granulate (pH=5.53) on a suitable tableting machine (tablet weight 713 mg, punch diameter 10 mm, hardness 80 N). Despite the use of water to aid in the mixing, these tablets did not turn pink upon storage under accelerated conditions (40°C/ 75%RH) packaged in PVC/PE/PVDC - aluminium blisters or in HDPE containers.

## Example 2

## Granulate of Paroxetine mesylate for tablets

The process as in Example 1 was maintained with the modification that the steps 3 and 4 are performed simultaneously, at 40 °C. The time necessary for adding the paroxetine mesylate aqueous solution is approx. 15 minutes; for drying approx. 45 minutes. The composition has a pH of 5.37.

## Example 3

Tablets of paroxetine mesylate are made having the following composition:

Paroxetine mesylate	12.915mg (10 mg equiv.)	25.83 mg (20 mg equiv.)	38.745 mg (30 mg equiv.)	51.66 mg (40 mg equiv.)
Calcium hydrogen phosphate anhydrate pH 5.1	158.88mg	317.75mg	476.64mg	635.50mg
Sodium starch glycollate	2.975mg	5.95mg	8.925 mg	11.90mg
Magnesium stearate	3.50mg	7.00mg	10.50mg	14.00mg

10

The tablets are made as follows. Paroxetine mesylate is mixed with calcium hydrogen phosphate. 10 % water is added and the mixture granulated and dried to an added water content of around 1%. The resulting granulate is mixed with the sodium starch glycollate, and magnesium stearate in a free fall mixer and compressed into tablets; each tablet having the above composition. The pH varies from 5.2 to 5.8 depending upon the batches of excipients used.

15

## Example 4

## Tablets of Paroxetine mesylate

20	Paroxetine mesylate	51.66 mg (equivalent to 40 mg of paroxetine free base)
	Calcium hydrogen phosphate	411.83 mg
	Microcrystalline cellulose	213.92 mg
	Sodium starch glycollate	28.52 mg
25	Magnesium stearate	7.13 mg



Tablets having the above composition are made as follows. Paroxetine mesylate is mixed with calcium hydrogen phosphate. 10 % water is added and the mixture granulated and dried to an added water content of around 1%. The resulting granulate is mixed with microcrystalline cellulose, sodium starch glycollate, and magnesium stearate in a free fall mixer and compressed into tablets; each tablet having the above composition. The pH is 5.45.

#### Example 5

The same tablets as Example 4 are made, but first a paroxetine mesylate aqueous solution having a paroxetine mesylate concentration of about 30 wt% is formed. This solution is added to microcrystalline cellulose and dried to form a granulate. The produced granulate is mixed with calcium hydrogen phosphate, sodium starch glycollate, and magnesium stearate in a free fall mixer and compressed into tablets. The pH is 5.26.

#### Example 6

##### Tablets of Paroxetine mesylate

##### Composition per 1 g of tablet core:

20	Paroxetine mesylate	72 mg
	Mannitol	300 mg
	Calcium hydrogen phosphate	533 mg
	Croscarmellose sodium	20 mg
	Povidone	30 mg
25	Magnesium stearate	15 mg

1. Granulate 30 % solution of paroxetine mesylate with a pre-blend mixture of mannitol, calcium hydrogen phosphate and croscarmellose sodium and dry to water content less than 1 %.
2. Mix the dried and screened granulate with povidone and magnesium stearate. The granulate is suitable for compression into tablets containing 20 mg paroxetine.

## Example 7

Tablets of Paroxetine mesylate

Composition of 1 g of tablet core:

5	Paroxetine mesylate	72 mg
	Microcrystalline cellulose	290 mg
	Calcium hydrogen phosphate	580 mg
	Sodium starch glycollate	28 mg
	Hydroxypropyl cellulose	20 mg
10	Magnesium stearate	10 mg

1. Granulate 30 % aqueous solution of paroxetine mesylate with a pre-blend mixture of microcrystalline cellulose, calcium hydrogen phosphate and sodium starch glycollate and dry.
- 15 2. Mix the dried and screened granulate with hydroxypropyl cellulose and magnesium stearate.

The granulate is suitable for compression into tablets containing 20 mg paroxetine and having a pH of 5.14.

- 20 In the following Examples 8-19, the compositions listed are processed substantially as in Example 1, e.g. a granulate is prepared by using a concentrated aqueous solution of paroxetine mesylate and the dry paroxetine mesylate-containing granulate with water content less than 1 % is mixed with the remaining excipients to prepare a bulk material for processing into the listed final forms by conventional  
25 methods.

## Example 8

Composition of effervescent tablets (per 1 g)

## a) granulate

Paroxetine mesylate 26 mg

5 Mannitol 166 mg

## b) Effervescent system

Sodium bicarbonate 378 mg

Citric acid anhydrous 400 mg

Saccharin sodium 9 mg

10 Aspartame 3 mg

Sodium chloride 1.5 mg

Sodium lauryl sulfate 0.05 %

Flavour 16 mg

## 15 Example 9

Composition of effervescent tablets (per 1 g)

## a) granulate

Paroxetine mesylate 26 mg

Isomaltose 203 mg

## 20 b) Effervescent system

Sodium bicarbonate 336 mg

Citric acid 400 mg

Sodium chloride 1.5 mg

Neo-DHC 5 mg

25 Sodium lauryl sulfate 0.5 mg

Flavour 18 mg

## Example 10

Composition of dispersible tablets (per 1 g)

## 30 a) granulate

Paroxetine mesylate 72 mg

Pregelatinized starch 380 mg

Microcrystalline cellulose 380 mg

Sodium starch glycollate 100 mg

	b) Other excipients	
	Hydroxypropyl cellulose	20 mg
	Sodium saccharin	8 mg
	Sodium stearyl fumarate	10 mg
5	Colloidal silicic dioxide	10 mg
	Flavour	20 mg

## Example 11

Composition of dispersible tablets (per 1 g)

10	a) granulate	
	Paroxetine mesylate	72 mg
	Mannitol	500 mg
	Microcrystalline cellulose	260 mg
	Crosspovidone	100 mg
15	b) Other excipients	
	Sodium saccharin	8 mg
	Sodium stearyl fumarate	10 mg
	Colloidal silicon dioxide	10 mg
	Flavour	20 mg

20

## Example 12

Composition of sublingual tablets (per 1 g)

	a) granulate	
	Paroxetine mesylate	72 mg
25	Sucrose	650 mg
	Sorbitol	258 mg
	b) Other excipients	
	Sodium stearyl fumarate	20 mg

30

## Example 13

Composition of sublingual tablets (per 1 g)

## a) granulate

	Paroxetine mesylate	72 mg
5	Mannitol	318 mg
	Microcrystalline cellulose	600 mg

## b) Other excipients

	Magnesium stearate	10 mg
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## 10 Example 14

Composition of controlled release tablets with hydrophilic matrix (per 1 g)

## a) granulate

	Paroxetine mesylate	72 mg
	Hydroxypropylmethyl cellulose	700 mg
15	Hydroxypropyl cellulose	168 mg

## b) other ingredients

	Povidone	40 mg
	Sodium stearyl fumarate	20 mg

## 20 Example 15

Composition of controlled release tablets with hydrophobic matrix (per 1 g)

## a) granulate

	Paroxetine mesylate	72 mg
	Microcrystalline cellulose	520 mg

## 25 b) other ingredients

	Glyceryl behenate	200 mg
	Glyceryl palmitostearate	200 mg
	Sodium stearyl fumarate	8 mg

## Example 16

Composition for immediate-release hard-shell capsules (per 1 g)

## a) granulate

	Paroxetine mesylate	72 mg
5	Maltodextrin	820 mg
	Pregelatinized starch	80 mg

## b) other ingredients

	crosspovidone	20 mg
10	colloidal silicone dioxide	8 mg

The produced granulate should be sieved and filled per 333 mg into Size 2 capsule.

## Example 17

Composition for enteric-release hard-shell capsules (per 1 g)

## 15 a) granulate

	Paroxetine mesylate	72 mg
	Sucrose-starch non-pareill seeds	790 mg
	Eudragit L 30 D 55	123.5 mg

## b) other ingredients

20	talc	7 mg
	polyethylene glycol 6000	7 mg
	silicone dioxide	0.5 mg

The produced granulate should be sieved and filled per 333 mg into Size 2 capsule.

25

## Example 18

Composition for controlled release hard-shell capsules (per 1 g)

## a) granulate

	Paroxetine mesylate	72 mg
30	microcrystalline cellulose	850 mg
	Ethylcellulose	60 mg
	Hydroxypropylcellulose	18 mg

## b) other ingredients

none

The produced granulate should be sieved and filled per 350 mg into Size 2 capsule.

Example 19

5 Composition for oral sachets (per 1 g)

a) granulate

Paroxetine mesylate	5 mg
Sucrose	565 mg
Mannitol	377 mg
10 Povidone	28 mg

b) other ingredients

saccharin sodium	10 mg
Flavour	15 mg

15 The invention having been described, it will be readily apparent to those skilled in the art that further changes and modifications in actual implementation of the concepts and embodiments described herein can easily be made or may be learned by practice of the invention, without departing from the spirit and scope of the invention as defined by the following claims.

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## CLAIMS

- 5           1. A solid paroxetine composition comprising a paroxetine salt and an excipient wherein said composition has a pH of 6.5 or less.
2. The composition according to claim 1, wherein said pH is within the range of about 4.5 to 6.5.
- 10           3. The composition according to claim 1, wherein said paroxetine salt is a paroxetine sulfonate salt or a paroxetine hydrochloride salt.
4. The composition according to claim 3, wherein said pH is less than 6.0.
- 15           5. The composition according to claim 3, wherein said pH is within the range of about 4.5 to 6.5.
6. The composition according to claim 5, wherein said paroxetine salt is paroxetine methane sulfonate or paroxetine hydrochloride.
- 20           7. The composition according to claim 6, wherein said paroxetine salt is paroxetine methane sulfonate.
8. The composition according to claim 1, wherein the excipient is acidic calcium phosphate.
- 25           9. The composition according to claim 1, wherein said composition is a tablet and said paroxetine salt is contained in a pharmaceutically effective amount and is selected from paroxetine sulfonate salts and paroxetine hydrochloride salts.
- 30           10. The composition according to claim 9, wherein said excipient is selected from the group consisting of a diluent, a binder, a disintegrant, a lubricant, a colorant, or a combination of two or more thereof.



11. The composition according to claim 10, which does not contain a hydrosoluble or hydrophilic diluent.

5 12. The composition according to claim 11, which does not contain a taste masking coating.

13. The composition according to claim 11, which comprises calcium phosphate, a lubricant and a disintegrant.

10

14. The composition according to claim 13, wherein said paroxetine salt is paroxetine methane sulfonate salt.

15 15. A paroxetine solid dosage form comprising a paroxetine sulfonate salt and having been made with the aid of water.

16. The dosage form according to claim 15, wherein said dosage form is a tablet or a capsule.

20 17. The dosage form according to claim 16, wherein said paroxetine sulfonate salt is paroxetine methane sulfonate.

25 18. The dosage form according to claim 15, wherein said paroxetine sulfonate salt was combined as an aqueous solution with at least one excipient in preparing said dosage form.

19. The dosage form according to claim 18, wherein said dosage form has a pH of 6.5 or less.

30 20. A granulate formed by mixing water, paroxetine sulfonate, and at least one excipient and drying the resulting mixture.

21. The granulate according to claim 20, wherein said mixing was accomplished by adding together an aqueous solution of said paroxetine sulfonate salt with said at least one excipient.

5 22. The granulate according to claim 21, wherein said aqueous solution of paroxetine sulfonate salt is a concentrated solution having at least about a 10 wt% concentration of paroxetine sulfonate.

23. The granulate according to claim 22, wherein said aqueous solution has a  
10 paroxetine sulfonate salt concentration of at least about 30 wt%.

24. The granulate according to claim 20, wherein said mixing and said drying are carried out simultaneously.

15 25. The granulate according to claim 21, wherein said aqueous solution of paroxetine sulfonate was added to a powdered or granulated blend of said at least one excipient.

26. The granulate according to claim 20, wherein said granulate has an  
20 average remaining added water content of about 2.0 wt% or less.

27. The granulate according to claim 26, wherein said granulate has an average remaining added water content of about 1.0 wt% or less.

25 28. The granulate according to claim 27, wherein said granulate has an average remaining added water content of about 0.8 wt% or less.

29. The granulate according to claim 20, wherein said granulate composition exhibits a pH value of 6.5 or less.

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30. The granulate according to claim 29, wherein said granulate has a pH of about 6.0 or less.

31. The granulate according to claim 29, wherein said granulate has a pH within the range of 4.5 to 6.5.

32. The granulate according to claim 20, wherein said paroxetine sulfonate salt is paroxetine methane sulfonate.

33. A process, which comprises:  
mixing an aqueous solution containing at least 10 wt % of a paroxetine sulfonate with at least one solid excipient; and  
drying to form a granulate.

34. The process according to claim 33, wherein said drying step produces a granulate having a remaining added water content of about 2.0 wt% or less.

35. The process according to claim 34, wherein said drying step produces a granulate having a remaining added water content of about 1.3 wt% or less.

36. The process according to claim 35, wherein said drying step produces a granulate having a remaining added water content of about 1.0 wt% or less.

37. The process according to claim 36, wherein said drying step produces a granulate having a remaining added water content of about 0.8 wt% or less.

38. The process according to claim 33, wherein said aqueous solution concentration of said paroxetine sulfonate is at least 30 wt%.

39. The process according to claim 38, wherein said aqueous solution concentration of said paroxetine sulfonate is at least 40 wt%.

40. The process according to claim 33, wherein said mixing and drying steps are performed concurrently.

41. The process according to claim 33, wherein said solid excipient is a granulate.

42. The process according to claim 33, which further comprises optionally mixing additional excipients with said granulate and pressing said granulate composition into a tablet.

5

43. The process according to claim 42, which further comprises film coating said tablet.

44. The process according to claim 33, which further comprises filling said granulate into a capsule or sachet.

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45. The process according to claim 33, which further comprises processing said granulate into effervescent tablets, sublingual tablets, controlled release tablets or delayed release tablets.

15

46. The process according to claim 33 wherein the excipients comprise at least one ingredient selected from the group consisting of binders, disintegrants, and fillers.

47. The process according to claim 46, wherein said granulate exhibits a pH value of 6.5 or less.

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48. The process according to claim 47, wherein said granulate has a pH of about 6.0 or less.

49. The process according to claim 47, wherein said granulate has a pH of about 5.5 or less.

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50. The process according to claim 33, wherein said paroxetine sulfonate is paroxetine methane sulfonate.

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